REMARKS

The Examiner provides a number of rejections and we list them here in the order in which they are addressed:

I. 35 USC § 112 Rejections
   - A. Claims 111-116 are rejected because the specification as filed allegedly does not provide an adequate written description.
   - B. Claims 111-116 are rejected as allegedly lacking enablement.
   - C. Claims 111-116 are rejected as allegedly being indefinite.

II. 35 USC § 102(b)/(e) Rejections
   - A. Claims 111, 113, 115, and 116 are rejected as allegedly being anticipated by Yull *et al.*, *Procd. Natl. Acad. Sci USA* 92:10899-10903 (1995).
   - B. Claims 111, 115, and 116 are rejected as allegedly being anticipated by Nagasawa *et al.*, *Meiji Daigaku Ngakuku Kenkyu Hokoku* 100:13-21 (1994).
   - C. Claims 111, 113, 115 and 116 are rejected as allegedly being anticipated by Niemann *et al. J. Animal Breeding Genetics* 113:437-444 (1996).
   - D. Claims 111, 115, and 116 are rejected as allegedly being anticipated by Sympson *et al. J. Cell Biol.* 125: 681-693 (1994).
   - E. Claims 111, 115, and 116 are rejected as allegedly being anticipated by Sun *et al.* WO 96/93494 or *United States Patent No. 5,824,543* (1990).
   - F. Claims 111, 112, 115 and 116 are rejected as allegedly being anticipated by Paleyanda *et al. Trangenic Res.* 3:334-343 (1994).

III. The Examiner requests amendment of the invention title.

I. The Claims Comply With 35 USC § 112

A. The Examiner Has Misapplied Legal Standards

1. The Applicant Claims A Production Method, Not DNA Compositions

The Examiner provides a lengthy scientific discussion regarding urinary protein secretion. Most citations presented within this discussion were published after the Applicant's filing date and do not constitute proper references on which to base a statutory rejection. The Applicants, on the other hand, rely below upon teachings from references cited within the specification that show the understandings of those having ordinary skill in the art at the time the application was filed.

The Examiner has summarized the overall rejection as follows:

> Thus, claiming a method of expressing and secreting a protein into the urine of a mammal using any promoter of the uromodulin, uropontin, osteopontin, nephrocalcin ... gene[s] ...without defining the specific structure of the promoter that has that function is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel,* 15 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. V. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

Office Action, pg. 13. The Applicants are familiar with this case law and believe that the Examiner has inappropriately expanded the Court's holdings of these cases. In both cases, the Examiner has misapplied these holdings. The Applicants point out that these cases provide guidance regarding written description only for claims directed to DNA compositions (*i.e.*, nucleic acid sequences):

> The present count is to a product, a DNA which codes for B-IF; it is a claim to a product having a particular biological activity or function ... such a product is not conceived until one can define it other than by its biological activity for function.

Fiers at 1169. The Applicant does not present any product claims comprising DNA compositions. Consequently, *Fiers* is not helpful to support the Examiner's conclusion.

In *Eli Lilly*, the Federal Circuit found claims drawn to vertebrate and mammalian insulin cDNAs invalid because the written description did not support broad generic claims. The patent disclosed the sequence of rat insulin cDNA. The court stated that "an adequate written description of a DNA 'requires a precise definition, such as by structure, formula, chemical name, or physical properties' not a mere wish or plan for obtaining the claimed chemical invention."[1] The court held that disclosure of the sequence for a single species of insulin cDNA, the rat insulin cDNA, did not provide adequate written description to support broader generic claims to mammalian and vertebrate insulin cDNA. Consequently, *Eli Lilly* provides guidance regarding the requirements under which an Applicant may be granted DNA composition *genus claims*; not novel and unobvious method claims that only use specific promoter sequences (especially those that have already been disclosed in the art).

2. The Examiner Erroneously Concludes The Specification Does Not Teach Protein Secretion

The Examiner's case rests upon an erroneous conclusion that the Applicant's have not shown that the claimed promoters will secrete proteins into urine:

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[1] *Eli Lilly*, 119 F.3d at 1566 (citing *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993)).

> ... applicants have not shown that ... uromodulin, osteopontin, uropontin, nephrocalcin promoter as currently claimed would secrete exogenous protein in their urine. Applicants have not provided adequate written description that ... expressing proteins in cells of the urinary tract will secret the exogenous protein in their urine.

Office Action, pg 15. The Applicants present below teachings from the specification and the cited references showing that the Examiner's conclusion is simply wrong. Almost all these citations were identified to the Examiner in the last Office Action response.

3. The Examiner Improperly Insists On Knowing A Mechanism

The Examiner has based the rejection on a misperception that the Applicant must disclose the actual promoter structure and/or sequence responsible for protein secretion, and explain its function, in order to obtain the pending claims:

> Applicants have not shown that the uromodulin, osteopontin, nephrocalcin ... promoters had the appropriate signal sequence that would cause secretion into the urine as claimed ...

Office Action, pg. 15. The Applicants remind the Examiner that an understanding of operative mechanism is irrelevant to *any* inquiry into patentability. Indeed, it is well settled law that , "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *Newman v. Quigg*, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989). Furthermore, an inventor need not comprehend the scientific principles behind the invention as, "[a]n inventor's theory or belief as to how his invention works is not a necessary element to satisfy the enablement requirement." *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985). The Examiner, however, erroneously suggests that such an inquiry into mechanism is relevant, and, thereby, betrays a fundamental misunderstanding of U.S. patent law.

The Applicants present below intrinsic evidence (*i.e.*, that which is presented within the Applicants' specification) showing that one having ordinary skill in the art would understand that the Applicants' invention of using a specific promoter would work to secrete proteins into the urine. The evidence below shows that the Applicants' claimed promoters are derived from kidney-specific genes encoding proteins or enzymes that are secreted into urine. This evidence, alone, is sufficient to show operability and satisfies the legal standards for written description as interpreted by the Federal Circuit.

3. The Examiner Inappropriately Suggests All Promoters Must Be Structurally Correlated

The Examiner states that "Applicants have not shown that uromodulin, osteopontin, uropontin, nephropontin ... [are] correlated structurally to the WAP or uroplakin promoters". *Office Action pg 15.* The Examiner provides no statutory basis for this requirement and the Applicants

believe the Examiner is confused and might be applying standards relevant to genus claims. The Applicants respectfully request the Examiner provide a legal authority on which this requirement is based or withdraw the basis.

B. The Claims Adhere To Written Description

1. Whey Acidic Protein (WAP) And Uroplakin Promoters

The Examiner admits that "WAP and uroplakin promoters (currently claimed) capable of expressing and secreting exogenous protein in the urine of a transgenic non-human mammal have adequate written description". *Office Action, pg. 4.* The Applicants point out that Claim 111 does recite "whey acidic protein" and "uroplakin" promoters.

Nevertheless, the Examiner is requested to note that the WAP and uroplakin promoters have been removed from Claim 111 and represented in new Claims 116-123.

2. ApoE, Epo, and Renin Promoters

The Examiner states that "... the specification and the art at the time of filing did not provide adequate written description that the ApoE, Epo or renin promoters were capable of expressing and secreting exogenous protein." *Office Action pg. 5.* The Applicants are confused as to why the Examiner provides almost four (4) complete pages devoted to unclaimed embodiments. The Applicants point out that this rejection basis is irrelevant because they are not directed to any claimed elements.

3. Uromodulin Promoters

The Examiner states that "Uromodulin ... promoters (currently claimed) capable of expressing and secreting exogenous protein into the urine of a transgenic non-human mammal lacks written description." *Office Action pg. 9.* The Applicants disagree.

The Examiner admits that a uromodulin promoter is taught on pp 26-27, 41 and within Examples 2 and 3, but ignores the Applicants' request to inspect pg. 21 ln 3 –19.[2] Applicants now provide the specification's full text for the Examiner's convenience:

> For instance, uromodulin or the Tamm-Horsfall protein (THP) is found in human urine in large quantities ... THP expression is specific only to the kidney ... The single human gene consists of 11 exons and 20 introns, the mRNA is about 2.6 kb in size (Hession *et al., Science* 237: 1479-1484, 1987; Pennica *et al., Science* 236:83-87, 1987). ... The leader sequence suggests that the majority of THP is a secreted protein ... THP was originally isolated from the urine of pregnant women ... It is also present in the urine from males ...

Applicants' Specification, pg. 21 ln 1 – 21 [emphasis added]. Despite the fact that the specific functions of each exon may, or may not have been known, the Examiner is reminded that it is not necessary to understand the mechanism of an invention in order to obtain claims to the disclosed invention.

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[2] See previous Office Action response pg. 6.

Further, the Examiner has misunderstood Yu *et al.*, "Bovine and rodent tamm-horsfall protein (THP) genes: cloning, structural analysis, and promoter identification" *Gene Expr*, 4:63-75 (1994)). Yu *et al.* teaches the entire uromodulin promoter including exons 1 and 2. Specifically, Yu *et al.* teaches that exon 1 is noncoding (i.e., a regulatory region). The publication's abstract appears below for the Examiner's convenience:

> We have isolated bovine and rodent cDNA and genomic clones encoding the kidney-specific Tamm-Horsfall protein (THP). In both species **the gene contains 11 exons**, the first of which is noncoding. Exon/intron junctions were analyzed and all were shown to follow the AG/GT rule. A kidney-specific DNase I hypersensitive site was mapped onto a rodent genomic fragment for which the sequence is highly conserved in three species (rat, cow, and human) over a stretch of 350 base pairs. Primer extension and RNase protection analysis identified a transcription start site at the 3' end of this conserved region. A TATA box is located at 32 nucleotides upstream of the start site in the bovine gene and 34 nucleotides upstream in the rodent gene. An inverted CCAAT motif occurs at 65 and 66 nucleotides upstream of the start site in the bovine and rodent genes, respectively. Other highly conserved regions were noted in this 350 bp region and these are likely to be binding sites for transcription factors. A functional assay based on an in vitro transcription system confirmed that the conserved region is an RNA Pol II promoter. The in vitro system accurately initiated transcription from the in vivo start site and was highly sensitive to inhibition by alpha-amanitin at a concentration of 2.5 micrograms/ml. These studies set the stage for the further definition of cis-acting sequences and trans-factors regulating expression of the THP gene, a model for kidney-specific gene expression..

The Examiner must now realize that one having ordinary skill in the art understood the nucleic acid structure of the uromodulin promoter and that the uromodulin promoter was capable of supporting protein secretion into the urine, albeit not in the context of a transgenic animal. Consequently, the Applicants' specification provides an adequate written description for a uromodulin promoter.

4. Uropontin/Osteopontin Promoters

The Examiner states that "... uropontin, osteopontin ... promoters (currently claimed) capable of expressing and secreting exogenous protein into the urine of a transgenic non-human mammal lacks written description." *Office Action pg. 9.* The Applicants disagree.

The Examiner admits that a uropontin/osteopontin promoter is taught on pg 28 ln 3 – pg 29 ln 6, but ignores the Applicants' more relevant teachings. The Applicants request the Examiner to inspect the Applicants' specification which provides an adequate written description that osteopontin is secreted into the urine. The Examiner is again reminded that it is not necessary to understand the mechanism of an invention (*i.e.*, exactly how a protein is secreted into the urine) only that the mechanism is operable (*i.e.*, it works):

> [Osteopontin] ... mRNA is found at high levels in the kidney, the protein is synthesized and secreted into tubule fluid by the epithelium in the thick ascending loop of Henle and the distal convoluted tubules ... (Crivello et al., *J Bone Miner Res* 7: 693-699, 1992).

Applicants' Specification, pg. 24 ln 10 – 12. The Examiner has admitted that uropontin/ osteopontin genes were known in the art at the time the specification was filed. *Office Action pg 9.* Consequently, it is now clear that the specification has provided an adequate written description to support claims that the uropontin/osteopontin promoter was understood by those skilled in the art to secrete a protein into urine, albeit not in the context of a transgenic animal.

5. Nephrocalcin

The Examiner states that "... nephrocalcin ... promoters (currently claimed) capable of expressing and secreting exogenous protein into the urine of a transgenic non-human mammal lacks written description." *Office Action pg. 9.* The Applicants disagree. Specifically, the Examiner makes the following erroneous statement:

> The art at the time of filing did not teach the mouse nephrocalcin promoter or secretory signal that allowed expression and secretion of exogenous protein into the urine of transgenic mammals.

Office Action, pg. 12. The Examiner has again: i) ignored the Applicants last Office Action response identifying pg 23 ln 24 – pg. 24 ln 4 specifically describing nephrocalcin secretion into the urine; and ii) erroneously assumed that the mechanism of an invention must be known in order to obtain patent claims. In the first instance, the Applicants now present specification teachings disclosing that nephrocalcin is secreted into urine:

> Urine also contains nephrocalcin (NC) ... The elevation of urinary NC in patients with renal cell carcinoma is common ... Urinary levels of NC corresponded with disease progression in patients with metastatic disease.

Applicants' Specification, pg. 23 ln 25 – pg. 24 ln 1 [emphasis added]. The specification also cites Desbois *et al., J. Biol. Chem.* 269: 1183-1190, 1994 on pg 24 ln 3 which teaches that "An osteocalcin-related gene has been identified as the nephrocalcin gene in mice". This publication presents a kidney-specific nucleic acid sequence of the nephrocalcin gene (ORG)and teaches a regulatory exon 1 that is not present in bone osteocalcin:

> Sequencing of the ... kidney-specific PCR products revealed the existence of an additional exon at the 5' end (Fig. 2). This new first exon, 163-bp long, contained several ATG codons placed in a poor context for initiation of translation ... and all followed by stop codons, suggested that this exon was a noncoding exon.

Desbois et al., pg. 1187, rhc. This reference provides evidence that one skilled in the art at the time of filing the present application understood that the nephrocalcin gene comprised a kidney-specific 5' regulatory region (*i.e.*, a promoter) AND that nephrocalcin appears in urine.

6. The Promoter Claim Breadth Is Appropriate

The Examiner states that "... i.e., "a" uromodulin promoter lacks written description because one uromodulin promoter does not describe all uromodulin genes". *Office Action pg. 17.* The Examiner is reminded that the article "a" is traditional in U.S. patent claim drafting and may be interpreted as either singular or plural. Further, unless the Examiner finds the claimed embodiment anticipated or obvious (which has not happened) the Applicants contend that the present specification contains adequate written description for promoters that adheres to current patent law (*supra*):

> 35 USC 112 requires disclosure of only one mode of practicing the invention . . . [insistence] upon a boilerplate recitation in the specification that the specific embodiment shown was not meant to limit the breadth of the claims, or that the example given was only one of several methods which could be employed. . . . is here an exaltation of form over substance."

In re Rasmussen, 211 USPQ 323, 327 n.7 (CCPA 1981). The Applicants respectfully request the Examiner to withdraw this rejection.

7. Enzyme Functionality Is Not A Patentability Issue

The Examiner improperly imports limitations into the Applicant's claims by stating that:

> The specification does not provide adequate written description for any transgenics that express and secretes enzymes in their urine. While the specification teaches a number of enzymes in Fig. 7, expression of such enzymes in the urinary tract of a transgenic mammal may cause an alteration in the phenotype of the mammal. In addition, expression of such enzymes in the urinary tract of a transgenic mammal may cause the enzyme to be non-functional.

Office Action pg. 18. The Applicants' remind the Examiner that the pending claims do not recite any functional requirement for a secreted protein or enzyme. Further, it is well settled patent law that a claim may contain many inoperable elements (even though the Applicant believes this not to be the case):

> ... the mere possibility of inclusion of inoperative . . . [subject matter] does not prevent allowance of broad claims ... many patented claims read on vast numbers of inoperative embodiments.

Application of Cook, 439 F.2d 730, 734, n4, 735169 U.S.P.Q. 298 (CCPA 1971), and

> Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude . . . possible inoperative substances. . . .'

Atlas Powder Co. v. E.I. Du Pont de Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409 (Fed. Cir. 1984). Consequently, even if the Examiner is correct that some enzymes may not be functional (which is highly speculative), this is not an appropriate basis on which to reject the present claimed embodiment. The Applicants respectfully request the Examiner to withdraw the present rejection.

8. The Claims Do Not Contain New Matter

The Examiner believes several elements now within the claimed embodiments represent new matter. The Applicants are surprised at this new basis of rejection and believe that the Examiner is looking for exact phraseology within the specification that mimic the new claims (*i.e.*, possibly analogous to the European standards). That is not the law in the United States. The Federal Circuit has clearly stated otherwise:

> In order to satisfy the written description requirement, the disclosure as originally filed need not provide in haec verba support for the claim subject matter at issue.

Fujikawa v. Wattansasin, 93 F.2d 1559, 1570, 39 USPQ2d 1895, 1904 (Fed.Cir. 1996) [emphasis added],

and,

> It is not necessary that the application describe the claim limitations exactly, . . . but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that appellants invented processes including those limitations.

In re Wertheim, 191 USPQ 90, 96 (CCPA 1976). The Applicants argue that the identified specification support below adheres to these legal standards.

a. Urinary Tract Cells And Their Transfection Is Not New Matter

The Examiner states that:

> The specification as originally filed did not teach or suggest introducing the nucleotide sequence into the urinary tract cells to create a transgenic non-human mammal as broadly claimed in new claim 111.

Office Action pg 19 and,

> The specification as originally filed does not contemplate the concept of "a plurality of urinary tract cells" in claim 111. Support for the concept has not been provided and none can be found in the specification as originally filed.

Office Action pg 19. The Applicants disagree and direct the Examiner to the following teachings within the specification:

> In yet another embodiment, the invention relates to a gene construct for use in transgenic animals ... that results in the expression of said DNA sequence in the urinary tract cells; wherein ... said gene construct ... obtain[s] the production of said peptide or protein in urinary tract cells and secretion into urine of an animal.

Applicants' Specification pg 15 ln 7 – 20 [emphasis added]. Further, the specification provides an even broader teaching:

> In an additional embodiment, this invention provides a non-human male or female transgenic animal comprising cells having incorporated expressibly therein a polynucleotide encoding a complex protein or peptide that is produced in the urine. This gives an unique opportunity to utilize the urinary tract as a site from production of recombinant proteins.
> ...
> The regions of urinary tract include the kidneys ... The cells of the kidneys ... are the epithelial cells ...

Applicants' Specification pg 15 ln 21 – 35 [emphasis added]. Consequently, the Applicants respectfully request the Examiner withdraw the new matter rejections predicated upon "a plurality of urinary tract cells".

b. Uropontin Promoter Is Not New Matter

The Examiner states that "Support for the uropontin promoter in claim 111 has not been provided and none can be found in the specification as originally filed." *Office Action pg 19.* The Applicants disagree and point the Examiner to the following teaching in the Applicants' specification appearing on pg 29 ln 24-27: "For instance, the urinary tract-specific regulatory sequences of the ... uropontin ... genes are preferred ...". Consequently, the Applicants respectfully request the Examiner to withdraw this new matter rejection.

c. Human Protein C Is Not New Matter

The Examiner states that "The limitation of "human" protein C in claim 112 is new matter." *Office Action pg 19.* The Applicants disagree and point the Examiner to Figure 3 which discloses the WAP/HPC construct (Fig. 3A) and the structure and function of HPC (Fig. 3B). Consequently, the Applicants respectfully request the Examiner to withdraw this new matter rejection.

d. Claim 113 Is Not New Matter

The Examiner states that "A protein comprising "prothrombin, Factor VII ... and albumin: in claim 113 is new matter because the phrase does not have support in the specification as originally filed. *Office Action pg 20.* The Applicants disagree and point the Examiner to the

Applicants' specification on pg 30 ln 24 – 27 which identifies these specific proteins. Consequently, the Applicants respectfully request the Examiner to withdraw this new matter rejection.

e. Claim 114 Is Not New Matter

The Examiner states that "A protein comprising "phytase, phosphate removing enzyme ... and phenylacetaldehyde dehydrogenase" in claim 114 is new matter because the phrase does not have support in the specification as originally filed." *Office Action pg 20.* The Applicants point out an apparent lack of consistency by the Examiner. The Examiner is reminded that on page 19 of the current Office Action there is an admission stating that: "Support for the enzymes of claim 114 are found in Fig. 7". The Applicants contend that support for all the proteins and enzymes in Claim 114 can be found in Figure 7. Consequently, the Applicants respectfully request the Examiner to withdraw this new matter rejection.

f. Claim 116 Is Not New Matter

The Examiner states that "The concept of claiming the urine of a transgenic mammal as in claim 116 is new matter. Support for claiming the urine cannot be found in the specification as originally filed. *Office Action pg 20.* The Applicants disagree and now point to illustrative examples where the Applicants' contemplate that transgenic urine comprises one embodiment of the present invention:

> Urine alone or mixed with feces and other wastes produced by the transgenic animal may be collected ...

Applicants' Specification, pg. 18 ln 19-21, and

> Urine was collected from transgenic mice and dialyzed. ... Dialyzed urine samples were diluted ... to raise the level of detection.

Applicants' Specification, pg 38 ln 16-27. Consequently, the Applicants respectfully request the Examiner withdraw this new matter rejection.

B. The Claims Are Enabled

The Examiner makes several allegations that the claims are not enabled by the Applicants' specification. The Applicants disagree. Before addressing each rejection basis, the Applicant provides legal authority describing that a patent application has a presumption of enablement:

> Enablement requires that the application "contain a description that enables one skilled in the art to make and use the claimed invention" *Atlas Powder Co. v/ E.I. duPont De Nemours & Co.*, 750 F.2d 1469, 1576 (Fed. Cir. 1984). "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first

> paragraph of § 112 unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi,* 58 C.C.P.A. 1069, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

Fiers v. Revel, 984 F.2d 1164, 1171 (Fed. Cir. 1993). The Examiner has not provided any reasons to doubt the objective truth of the Applicants' specification. Instead, the Examiner provides mere conclusory statements without referring to any evidence that the Applicants' reliance on the skill of one having ordinary skill in the art to perform certain methods is misplaced.

It is incumbent upon the Examiner to establish a *prima facie* case of lack of enablement.[3] The test of enablement is:

> ... whether one skilled in the art could *make* or *use* the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation.[4] The specification is enabling of the claims if "experimentation is ... *routine*, or if the specification provides a *reasonable amount of guidance* on the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed."[5]

The Examiner is reminded that it is axiomatic that when the claims depend upon experimentation that is within the capability of one having ordinary skill in the art, that these details need not appear in the specification. Applicants assert that a *prima facie* case of non-enablement continues to be deficient.

1. Uromodulin, Uropontin, Osteopontin, And Nephrocalcin

The Examiner states that the specification: i) "... does not reasonably provide enablement for using uromodulin, uropontin, osteopontin, nephrocalcin ... promoter to obtain expression and secretion of exogenous protein [or enzymes] in the urine of transgenic non-human mammals ... " *Office Action pg 20,* and ii) "... does not enable expressing and secreting an exogenous protein into the urine of a transgenic non-human mammal using any uromodulin, uropontin, osteopontin, nephrocalcin ... promoter." *Office Action pg. 21.*

The Applicants disagree and remind the Examiner that the specification provides evidence (*i.e.*, both Applicants' statements and cited scientific research publications) demonstrating that genes comprising these promoters and their respective gene products were understood by those having skill in the art to be expressed within kidney cells and secreted into the urine (see Written Description section, *supra*), albeit not in the context of a transgenic

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3 *In re Marzocchi,* 169 USPQ 367, 370 (CCPA 1971).

4 MPEP 2164.01, citing *United States v. Telectronics, Inc.,* 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988); *In re Stephens,* 529 F.2d 1343, 188 USPQ 659 (CCPA 1976) [emphasis added].

5 *Ex parte Forman,* 230 USPQ 546 (BPAI 1986)[emphasis added]; see also, *In re Wands,* 8 USPQ.2d 1400, 1414 (CAFC 1988)

animal. The Examiner has not provided any evidence demonstrating that these statements and research publications are objectively untruthful.

The Applicants' specification also provides sufficient guidance for various types of methods by which a non-human mammal may receive, and incorporate, exogenous DNA. For example:

> Genes may be introduced into an organism in accordance with the invention using standard, well-known techniques for the production of transgenic organisms. These techniques have been the subject of numerous books, including for instance, *TRANSGENESIS TECHNIQUES* , Murphy et al., Eds., Human Press, Totowa, New Jersey (1993). *GENETIC ENGINEERING OF ANIMALS*, A. Puhler, Ed., VCH Verlagsgesellschaft, Weinheim, New York (1993) and *Transgenic Animal Technology,* C.A. Pinkert, Ed., Academic Press, Inc., San Diego, (1994), which are incorporated by reference herein in their entirety.

Applicants' Specification, pg 31 ln 11 – 20. Clearly, the Federal Circuit expects the Examiner to provide evidence that the methodologies within these books are not correct in order to maintain a lack of enablement rejection when the Applicants rely upon knowledge that is known at the time of filing the specification. The Applicants argue that the Examiner, has not, and can not, do so.

The Applicants provide additional detail regarding the content of these scientific treatises by specifically identifying particularly popular techniques:

> For instance, DNA can be introduced into totipotent or pluripotent stem cells by microinjection, calcium phosphate mediated precipitation, liposome fusion, retroviral infection or by other means. DNA delivery by electronic pulse into swine oocytes and embryos (Yang *et al., Cell Res.* 7: 39-49, 1997).

Applicants' Specification, pg 32 ln 21 – 25. The Applicants argue that the specification provides sufficient evidence that one having ordinary skill in the art would understand that transgenic techniques at the time the specification was filed did NOT require undue experimentation.[6] Consequently, the Applicants claimed promoters are enabled. The Applicants respectfully request the Examiner withdraw the rejection.

2. Transgenic Non-Human Animals

The Examiner states that "Claims 111-116 are not enabled because the specification does not provide adequate guidance for one of skill to make transgenic pigs, sheep, goats, cows, rabbits, or horses." *Office Action pg 21.* The Applicants remind the Examiner of the above argument in the

[6] "The key word is 'undue' not 'experimentation.'" *In re Angstadt and Griffin*, 190 USPQ 214, 219 (CCPA 1976). Indeed, "a considerable amount of experimentation is permissible . . . if the specification in question a reasonable amount of guidance with respect to the direction in which the experimentation should proceed . . . ." *Ex parte Jackson*, 217 USPQ 804, 807 (Bd. App. 1982); *In re Wands*, 8 USPQ 2d 1400, 1404 (CAFC 1988).

Written Description section (*supra*) presenting case law supporting the conclusion that when those having ordinary skill in the art understand the required techniques, a patent application does not require explicit enablement for all potential embodiments. That is the case here. The Applicants also cite various scientific treatises above summarizing and describing various successful transgenic techniques in many different species known to those having ordinary skill in the art at the time this specification was filed.

Specifically, the Applicants describe nuclei transfer from cells into embryos and provide numerous literature citations attesting to success in cows, pigs, and sheep. *Applicants' Specification pg 33 ln 15 – 25.* Other cited successful transgenic techniques utilized goat, rabbits, birds, fish, invertebrates, *D. melanogaster* (*i.e.*, a fruitfly), mice, and rats using another scientific treatise reference: *Transgenic Animals: Generation and Use,* Ed. L.M. Houdebine, Haywood Academic Publishers, The Netherlands, 1997). *Applicants' Specification, pg 33 ln 15 – pg 34 ln 6.*

The Applicants argue that there is sufficient evidence within the specification's cited references that demonstrate that one having ordinary skill in the art would understand how to successfully make a transgenic animal of any species. Consequently, the Applicants respectfully request the Examiner withdraw this rejections.

3. Enzyme Functionality

The Examiner states that: "The specification does not enable expressing enzymes in the urine of transgenic mammals (claim 114)". *Office Action pg 22.* The Applicants disagree for the same reasons argued above in relation to the Examiner's Written Description rejection. Briefly, the claims do not require enzyme functionality and it is well settled patent law that a claim is patentable and valid even though it may encompass inoperable embodiments (which the Examiner has not proved to be the case here).

Consequently, the Applicants respectfully request the Examiner withdraw this rejection.

C. The Claims Are Not Indefinite

The Examiner has rejected Claims 113 & 114 due to a claim construction interpretation by the Applicants' use of the term "comprising". The Applicants disagree with the Examiner's conclusion that the pending claims are indefinite. Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have amended Claims 113 and 114 to recite a Markush group. This amendment is made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

The Examiner has rejected Claim 115 because it is apparently dependent upon Claim 111 as a method claim. The Applicants disagree because Claim 111 does produce a transgenic non-human mammal, thereby making Claim 115 properly constructed. Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims,

Applicants have amended Claim 115 to describe the transgenic non-human mammal. This amendment is made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

The Examiner has rejected Claim 116 because it is apparently dependent upon Claim 111 as a method claim. The Applicants disagree because Claim 111 does recite transgenic urine, thereby making Claim 115 properly constructed. Nonetheless, without acquiescing to the Examiner's argument but to further the prosecution, and hereby expressly reserving the right to prosecute the original (or similar) claims, Applicants have amended Claim 115 to describe a protein produced by the method of Claim 111 present in the transgenic urine. This amendment is made not to acquiesce to the Examiner's argument but only to further the Applicants' business interests, better define one embodiment and expedite the prosecution of this application.

II. The Claims Are Not Anticipated

As the Examiner is well aware, a single reference must disclose each limitation of a claim in order for that reference to anticipate the claim. *Atlas Powder Co. v. E.I. du Pont De Nemours & Co.*, 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). This criterion is not met with the cited references.

The Examiner attempts to support the rejections by using "inherent anticipation". The Applicants wish to remind the Examiner of the strict Federal Circuit rules for framing this issue. To establish inherency, the cited references must show that the elements now at issue were implicitly present in the reference cited by the Examiner. For example, the Federal Circuit held that;

> [i]n relying upon the theory of inherence, the examiner must provide a basis in fact/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.

MPEP §2112, quoting *In re Robertson*, 169 F.3d 743 (Fed. Cir. 1999)(emphasis in original). The Examiner assumes that any transgenic animal allegedly comprising the WAP promoter will secrete a protein of interest into the urine. The Applicants point out that the Examiner argues against inherency when presenting 35 USC §112 ¶1 rejections:

> Obtaining exogenous protein expression in the kidneys, urinary tract or reproductive tract does not correlate to secreting the exogenous protein in the urine as claimed because expression does not guarantee the protein is secreted out of the cell and into the urine.

Office Action, pg. 5 [emphasis in original]. When framing these inherent anticipation rejections the Examiner advocates a contrary position:

> The WAP promoter inherently results in secretion of the protein in urine ... because the WAP promoter was known to cause expression in the kidney[7] ... and because Example 1 demonstrates the WAP promoter causes secretion of exogenous protein into the urine[8] .

Office Action, pg. 25. Two of the references supplied by the Examiner explicitly state that WAP will not even support expression of a protein of interest in the kidney (*i.e.*, Sympson *et al.* and Paleyanda *et al.*). The Examiner is reminded that the Court uses the term necessarily to mean "always or without fail". Clearly, those having skill in the art at the time this application was filed teach tissue-specificity for the WAP promoter. Paleyanda *et al.* provides a most telling conclusion:

> It is obvious that the longer mWAP promoter is not a 'perfect' one, due to limitations in tissue-specific and developmental regulation of HPC gene expression. We speculate that it will be difficult to find the 'perfect' promoter for mammary gland expression and that the combination of regulatory and transgene sequences, as well as, the post-translational modifications and biological activity of the expressed protein will determine the usefulness of transgenic animals as expression systems for therapeutic proteins.

Paleyanda et al., pg. 342 lhc. Consequently, Paleyanda *et al.* does not provide the teachings which the Examiner believes are present. Further, the Applicants object to the Examiner's arguing contrary patent law positions between the Written Description section and Anticipation section of the present Office Action.

Nevertheless, each reference below falls on its own because they do not meet the anticipation requirements.

A. Yull *et al.* Does Not Anticipate Claims 111, 113, 115 and 116

The Examiner states that "Yull taught a transgenic mouse whose genome comprised a sequence encoding Factor IX operatively linked to the WAP promoter. The WAP promoter caused expression of Factor IX in the milk". *Office Action pg 25.* The Applicants disagree and respectfully assert that the Examiner is just plain wrong. Yull *et al.* makes no mention of the WAP promoter. In fact, Yull *et al.* explicitly states that the promoter plasmid responsible for transgenic animal production is bovine β-lactoglobulin:

> DNA Constructs. The unmodified bovine β-lactoglobulin (BLG) construct, AATD, and FIXD have been described (9, 16). pRT-FIX was constructed by amplifying cDNA from mammary gland RNA from transgenic mouse BIX33.1, which expresses high levels of a ~ 1450-nt FIXD transcript (10). FIXDΔ3' was constructed by amplifying a segment of DNA from FIXD containing 5' BLG sequences ...

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7 The Examiner cites Paleyanda *et al.* for this proposition which, as argued below, is clearly an erroneous interpretation.

8 The Examiner is blatantly using impermissible hindsight. *W. L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1550, 220 USPQ 303, 311 (Fed. Cir. 1983).

Yull et al., pg 10899 rhc [emphasis added]. Clearly, the promoter sequences responsible for the FIX expression in Yull *et al.* are within the 5' BLG sequences. Because Yull *et al.* does not disclose a WAP promoter, the Examiner's reliance on Paleyanda *et al.* is of no moment.

Consequently, the Applicants respectfully request the Examiner withdraw this rejection.

B. Nagasawa *et al.* Does Not Anticipate Claims 111, 115, and 116

The Examiner states that "Nagasawa taught a transgenic mouse whose genome comprised a sequence encoding human Growth Hormone operatively linked to the WAP promoter. The WAP promoter caused expression of human Growth hormone in the milk." *Office Action pg. 26.* The Applicants disagree and respectfully assert that the Examiner is just plain wrong. Nagasawa *et al.* does not teach the detection of human growth hormone (hGH) in milk. Because Nagasawa *et al.* has not provided evidence that the hGH is secreted in these transgenic mice, the Examiner's inherency argument fails. As discussed above, the Examiner is not one of ordinary skill in the art and cannot assume to be true what is not disclosed by one who has ordinary skill in the art. Also, since Nagasawa *et al.* does not teach protein secretion, the Examiner's reliance on Paleyanda *et al.* is of no moment.

Consequently, the Applicants respectfully request the Examiner withdraw this rejection.

C. Niemann *et al.* Does Not Anticipate Claims 111, 113, and 116

The Examiner states that "Niemann taught a transgenic mouse whose genome comprised a sequence encoding Factor VIII operably linked to the WAP promoter. The WAP promoter caused expression of Factor VIII in the milk." *Office Action pg. 26.* The Applicants disagree and respectfully assert that the Examiner is just plain wrong. Niemann *et al.* does not teach the detection of Factor VIII in milk. In fact, Niemann *et al.* goes to great lengths to explain that just the opposite is true:

> Currently, determination of the presence of FVIII in sheep milk is under investigation.
> [and]
> We have attempted to detect FVIII activity in milk of transgenic mice and sheep by employing ELISA and two different clotting assays. ... these methods did not allow reliable detection of FVIII. ... in the present lambing season we will be able to clarify the question if or as to what extent the protein is secreted into the milk.

Niemann et al., pp.439 [last line]; pg. 441 [first full paragraph]. Applicants argue that since Niemann *et al.* provides contrary data in regards to the Examiner's major premise, the present anticipation rejection fails.

Consequently, the Applicants respectfully request the Examiner withdraw this rejection.

D. Sympson *et al* Does Not Anticipate Claims 111, 115, and 116

The Examiner states that "Sympson taught a transgenic mouse whose genome comprised ... a sequence encoding stromeylsin-1 operatively linked to the WAP (page 683, col 1 1st ¶). The WAP promoter caused expression of the protein in the milk (¶ bridging pg 683-684). The WAP promoter

inherently results in secretion of the protein in urine because the WAP promoter was known to cause expression in the kidney ... *Office Action pg 27.* The Applicants disagree and respectfully assert that the Examiner is just plain wrong. Sympson *et al.* explicitly teaches that the WAP promoter did NOT express in the kidney:

> The stromelysin-1 transgene was expressed in mammary glands of pregnant female mice (Fig. 1 C) ... but not in ... kidney ...

Sympson pg 683 rhc. Because Sympson explicitly contradicts the Examiner's speculation, the Examiner's inherency argument fails. Also, since Sympson teaches that kidney expression was not found, the Examiner's reliance on Paleyanda *et al.* is of no moment.

Consequently, the Applicants respectfully request the Examiner withdraw this rejection.

E. Sun *et al.* Does Not Anticipate Claims 111, 115, and 116

The Examiner states that "Sun taught transgenic mice whose genomes comprised a sequence encoding β-galactosidase operatively linked to the uroplakin promoter and obtaining expression of β-galactosidase in the urine and isolating the protein from the urine ..." *Office Action pg. 28.* The Applicants disagree because Sun presents no data detecting β-galactosidase in the urine or isolating β-galactosidase from the urine. The Examiner explicitly points to col 6 at ln 5 and ln 55 in the '543 patent. Column 6 ln 5 merely states that "The biologically active molecule can be isolated from the urine of these transgenic animals". This is an insufficient basis on which to establish anticipation.[9] Further, column 6 ln 55 (*i.e.*, Example 2) does not even mention urine comprising β-galactosidase. Consequently, the Examiner is improperly relying on a publication that is not enabled. A publication must be enabled to support an Examiner's anticipation rejection.[10]

Consequently, the Applicants respectfully request the Examiner withdraw this rejection.

F. Paleyanda *et al.* Does Not Anticipate Claims 111, 112, 115 and 116

The Examiner states that "Paleyanda taught making a mouse whose genome comprised a nucleic acid sequence encoding the human protein C operably linked to the WAP promoter. The human protein C was secreted into the milk of the mice". *Office Action pg 28.* The Applicants disagree and respectfully assert that the Examiner is just plain wrong. Paleyanda *et al.* does not teach the detection of human protein C in milk. Further, Paleyanda *et al.* explicitly teaches that human C protein is NOT expressed in kidney:

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9 Where earlier disclosures afford no more than a starting point and do not teach the art how to practice the new invention, they do not constitute anticipation. *Dewey & Almy Chemical Co. v. Mimex,* 124 F.2d 986, 989, 52 USPQ 138, 141 (CCPA1942).

10 In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'... ." *In re Hoeksema*, 399 F.2d 269, 158 USPQ 596 (CCPA 1968).

> Although rHPC transcripts were observed the kidney, the protein was not detected by immunohistochemistry. We can only speculate that this is due to inefficient translation of mRNA or rapid degradation of protein.

Paleyanda et al., pg 341 rhc. Because Paleyanda *et al.* has not provided evidence that the human protein C is secreted in these transgenic mice, the Examiner's inherency argument fails. As discussed above, the Examiner is not one of ordinary skill in the art and cannot assume to be true what is not disclosed by one who has ordinary skill in the art.

Consequently, the Applicants respectfully request the Examiner withdraw this rejection.

III. The Title Reflects The Claimed Embodiment

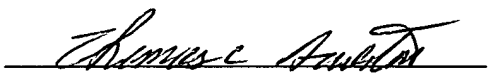
The Examiner states that "The title is not acceptable because no "compositions" are being claimed" *Office Action, pg. 2.* The Applicants believe this is an unnecessarily narrow interpretation of MPEP 606.01. Nevertheless, the title now is requested to read " Methods For Protein Expression In Transgenic Animal Urine".

The Applicants now respectfully request the Examiner withdraw the present objection.

CONCLUSION

The Applicants believe that the arguments and claim amendments set forth above traverse the Examiner's rejections and, therefore, request that all grounds for rejection be withdrawn for the reasons set above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the Applicants encourage the Examiner to call the undersigned collect at 617.984.0616.

Dated: August 17, 2005



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